The crucial role of thiamine in the development of syntax and lexical retrieval: a study of infantile thiamine deficiency

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This study explored the effect of thiamine deficiency during early infancy on the development of syntax and lexical retrieval. We tested syntactic comprehension and production, lexical retrieval abilities and conceptual abilities of 59 children aged 5–7 years who had been fed during their first year of life with a thiamine-deficient milk substitute. We compared them to 35 age-matched control children who were fed with other milk sources. Experiment 1 tested the comprehension of relative clauses using a sentence–picture-matching task. Experiment 2 tested the production of relative clauses using a preference elicitation task. Experiment 3 tested the repetition of various syntactic structures with various types of syntactic movement and embedding. Experiment 4 tested picture naming and Experiment 5 tested lexical substitutions in a sentence repetition task. Experiments 6 and 7 tested the children's conceptual abilities using a picture association task and a picture absurdity description task. The results indicated a very high rate of syntactic and lexical retrieval deficits in the group of children who were exposed to thiamine deficiency in early infancy: 57 of the 59 thiamine-deficient children examined had language impairment, compared with three of the 35 controls (9%). Importantly, unlike the impairment this group sustained in their language abilities, the conceptual abilities of most of the children were intact (only six children, 10%, were conceptually impaired). These findings indicate that thiamine deficiency in infancy causes severe and long-lasting language disorders and that nutrition may be one of the causes for language impairment.

Keywords: developmental language impairment; Hebrew; lexical retrieval; syntax; thiamine deficiency

Abbreviations: SLI = specific language impairment

Introduction

In November 2003, 20 infants were hospitalized in paediatric intensive care units in Israel with severe neurological symptoms, including lethargy, ophthalmoplegia, prolonged vomiting, nystagmus, seizures and coma. Brain MRI findings showed a bilateral symmetrical hyperintense signal in the basal ganglia, mamillary bodies and periaqueductal grey matter. The outcome of the infants was grave: two died of cardiomyopathy and approximately 10 remained with residual damage; one with complete atrioventricular block and permanent pacemaker, others with ataxia, sensorineural hearing loss, swallowing difficulties, severe epilepsy and
Thiamine and language development

According to the symptoms presented during the examination of one of these children, we suspected Wernicke’s encephalopathy due to thiamine deficiency. Analysis of the data accumulated on the affected infants yielded a single link between them: all had been fed with the same infant milk substitute formula (Fattal-Valevski et al., 2005). Suspecting the formula to be the source of this nationwide epidemic, it was tested by the Israeli Public Health Authorities. The test indicated that although the label of the container met the criteria for baby food and claimed to include 385 μg of thiamine (Vitamin B1), the formula did not in fact include thiamine (thiamine level was undetectable, < 0.5 μg/g). The manufacturer confirmed that they had indeed altered the formula and erroneously stopped adding thiamine to it in early 2003. Treatment with supplementary thiamine improved the infants’ condition.

The total number of children who consumed the defective formula nationwide was estimated to be between 600 and 1000 infants. Many of these children were considered neurologically ‘asymptomatic’ and had not displayed any neurological symptoms while being fed the thiamine-deficient formula and at the time the thiamine deficiency was discovered. They were, nevertheless, subject to routine follow-up as high-risk patients, and their development was monitored. The current study explored the language and conceptual abilities of 59 of these children, 5 years later.

Because thiamine plays a central role in cerebral metabolism and is an essential vitamin for brain development in infants (Butterworth, 1987; BÅ, 2005), there is a neurobiological basis to assume that thiamine deficiency would affect brain development, and as a result might also have effects on various abilities at a later age. Vitamins regulate brain development during foetal and early postnatal life, a fact that makes the brain particularly vulnerable to nutritional deficiencies (Georgieff, 2007). Thiamine serves as a cofactor for several enzymes involved primarily in carbohydrate catabolism (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and transketolase). These enzymes are important in the biosynthesis of a number of cell constituents including neurotransmitters (Haas, 1988), and for the production of reducing equivalents used in oxidant stress defences. Over and above its co-enzyme function in metabolism, thiamine also has a structural use (BÅ, 2008). It plays a role in membrane structure and function, including axoplasmic, mitochondrial and synaptosomal membranes, acts against agent-induced cytotoxicity and fixes membrane sites. It intervenes in synaptic transmission and plays a role in cellular differentiation, synapse formation, axonal growth and myellogenesis (Haas, 1988; BÅ, 2005, 2008). Bodily storage of thiamine is minimal, and symptoms involving the nervous and cardiovascular systems and the gastrointestinal tract appear in adults after just 2–3 weeks of thiamine deficiency in the diet (WHO, 1999). Thus, 3 weeks of thiamine deficiency is expected to affect brain development in infants.

Rat models indicate that maternal thiamine deficiency may indeed cause significant deficits in the spinal cord, brain enzymes, nerve conduction and diameter and myellogenesis (Trostler et al., 1977; Sanjeeva and Ramakrishnan, 1983; Claus et al., 1985; Fournier and Butterworth, 1990), and evidence has been found regarding thiamine involvement in synaptogenesis and nerve conduction (Matsuda et al., 1989; Ramakrishna, 1999). Deficits have also been reported in psychomotor and sensory abilities of pups (BÅ, 2005, 2008).

For human adults, the thiamine deficiency disease seen most often in the developed world is Wernicke’s encephalopathy (Wernicke, 1881; Thomson, 2008), which describes the effects in the acute phase, and later develops into Wernicke-Korsakoff’s syndrome in the chronic phase. Symptoms include confusion, ataxia, ophthalmoplegia and nystagmus, psychosis, confabulation and impaired memory retention and processing, graded according to the year of encoding, with old memories recalled better than new ones (Cermak and Moreines, 1976; Butters and Cermak, 1980; Ellis and Young, 1996; Baddeley, 1997). In severe cases, the patient may have seizures and fall into a coma. This disease mainly affects alcoholics, but can also occur in non-alcoholic patients with various diseases, disorders associated with malnutrition, and in individuals on ‘fad’ diets whose intakes are high in carbohydrate and low in thiamine (WHO, 1999; Ogershok et al., 2002; Fattal-Valevski et al., 2009a). It can also follow the consumption of foods such as betel nut and fermented fish, which contain anti-thiamin factors (Naing et al., 1969; Vimokesant et al., 1975; McGready et al., 2001).

Infantile thiamine deficiency has become a rare condition, at least in developed countries in which food has been enriched with vitamins (Thanangkul and Whitaker, 1966). It occurs mainly in breast-fed infants of mothers who have inadequate intake of thiamine (Butterworth, 2001; McGready et al., 2001). The onset of symptoms in infants is often very rapid and the fatality rate is high; death frequently occurs within a few days (Vasconcelos et al., 1999). Initially, an infant with thiamine deficiency has a normal appearance with varying degrees of constipation, occasional vomiting, crying and restlessness. Subsequently, the disease usually presents with cardiac manifestations or it may display meningeal irritation accompanied by vomiting and convulsions (pseudo-meningitic form). One infantile syndrome that might be related to thiamine deficiency is foetal alcohol syndrome. Although it has not directly been connected to thiamine deficiency, children with heavy prenatal alcohol exposure have been reported to display language impairments and auditory processing difficulties (Carney and Chermak, 1991; Abkarian, 1992; McGee et al., 2009; see also BÅ, 2009 for evidence suggesting that a part of deleterious actions of alcohol on foetal death is mediated by thiamine deficiency). At this point, nothing is known about the long-term effects on language and cognitive functioning of infantile thiamine deficiency.

When the thiamine-deficient children reported above were 2–3 years old, we started suspecting that their language was not developing as expected. A pilot assessment of 20 of these children showed a significant receptive and expressive language delay (Fattal-Valevski et al., 2009a). The aim of the current research was to evaluate in detail the effect of thiamine deficiency on the development of their language. The study thoroughly assesses the language abilities of 59 children who consumed this thiamine-deficient formula for a period that could deplete their thiamine storage.

Until now, there have been no data on nutrition or micronutrients as possible risk factors for syntactic and lexical impairments in children. Specifically, we do not know of any study on the
long-term outcomes of language in children who have suffered thiamine deficiency. This research enabled a rare view to the influence of nutrient deficiencies on the developing brain and the impact on language performance later in life. Thus, the current study assessed the syntactic and lexical retrieval abilities of children affected by the thiamine deficiency in defective milk formula to evaluate the long-term effects on language development. We focus on tests that are known to be sensitive clinical markers for children with syntactic or lexical specific language impairment, to see whether thiamine deficiency creates a language profile that is similar to that of specific language impairment.

**Classification and markers of specific language impairment**

The term 'specific language impairment' (SLI) refers to a heterogeneous group of children who show difficulties in various aspects of language: lexical retrieval, syntax, phonology, semantics and pragmatics (e.g. Bishop and Rosenblum, 1987; Clahsen, 1989; Rice and Wexler, 1996; van der Lely, 1997; Leonard, 1998; van der Lely and Christian, 2000; van der Lely, 1996, 1997, 1998; Bishop, 1997; Leonard, 1998; van der Lely and Christian, 2000; van der Lely and Battell, 2003; Friedmann and Novogrodsky, 2007, 2008, 2011; Schulz, 2010; Schulz and Roeper, 2011). In England, the Bercow Report (2008) indicated that ~7% of 5-year-olds going into school in 2007 had significant difficulties with speech and/or language. Several studies reported that within this heterogeneous group, subgroups can be identified according to the language component that is impaired (Rapin and Allen, 1983; Conti-Ramsden et al., 1997; Conti-Ramsden and Botting, 1999; Bishop et al., 2000; Bishop, 2006; Friedmann and Novogrodsky, 2007, 2008, 2011), and dissociations between linguistic abilities have been reported. For example, Dockrell et al. (2005) and Friedmann and Novogrodsky (2011) presented groups of children and adolescents with SLI whose word finding was impaired (lexical SLI) but who had preserved syntactic abilities; Friedmann and Novogrodsky (2004, 2007, 2011) reported a group of school-age children with SLI who had a syntactic deficit, but without lexical retrieval deficits and without phonological deficits. Friedmann and Novogrodsky (2008) also presented a group of children with a phonological deficit (phonological SLI), without a deficit in syntax. Thus, they suggested that subtypes of SLI exist, with impairments in different language domains and with different expressions. These types include syntactic SLI, with deficits in the comprehension and production of certain complex syntactic structures; lexical SLI impairment (also termed anoma or dysnomia)—a deficit in lexical retrieval; phonological SLI, possibly encompassing one or more of the following: phonological working memory, phonological input and output buffers, phonological rules and more; and pragmatic SLI, with deficits in discourse abilities. Schulz (2010) suggested another type of selective language impairment: a deficit in compositional semantics—semantic-SLI.

Children with a specific deficit in the lexical retrieval component show impaired access to lexical items, reflecting in failure to retrieve the target word, long hesitations, semantic or phonological paraphasias and circumlocutions in both spontaneous speech and naming tasks (Dockrell et al., 2001; Best, 2005; Dockrell and Messer, 2007; Friedmann and Novogrodsky, 2008). A picture naming task is a sensitive task for lexical retrieval difficulties, and we used this task in the current study. We also used a repetition task, because for some children with lexical retrieval difficulties even repetition yields word substitutions and omissions.

Children with a specific syntactic impairment encounter difficulties in understanding certain types of complex sentences. They show impaired comprehension of object relative clauses (Example 1, Adams, 1990; Stavrakaki, 2001; Friedmann and Novogrodsky, 2004, 2007, 2009, 2011), referential object questions (Example 2, Ebbels and van der Lely, 2001; Friedmann and Novogrodsky, 2003, 2011), and object topicalization (Example 3, van der Lely and Harris, 1990; Friedmann and Novogrodsky, 2003). (They also show a deficit in the comprehension of reversible verbal passives, Bishop, 1979; Adams, 1990; van der Lely and Harris, 1990, with better comprehension of adjectival passives, van der Lely, 1996. We did not include passives in the current study because of their scarcity in the input and output of Hebrew-speaking children, Berman, 1997; Jisa et al., 2002.)

1. **Object relative:** I know the girl that Daniel kissed __
2. **Object question:** Which girl did Daniel kiss __?
3. **Object topicalization:** This little girl, Daniel kissed __

All these impaired structures are derived by ‘syntactic movement’. Object relatives, object questions and topicalization structures are derived by movement of the object (in examples 1–3, ‘the girl’), across the subject (‘Daniel’), to the beginning of the clause. This movement results in a non-canonical order of the arguments in the sentence (namely, the agent of the action follows the theme of the action). This type of movement (termed ‘Wh-movement’ because it also creates Wh questions) has proved to be impaired in sentence comprehension and production in syntactic SLI (van der Lely and Harris, 1990; Friedmann and Novogrodsky, 2004, 2007; see also Bishop, 1979 for an earlier suggestion that the difficulty is in sentences in which the surface structure is different from the deep structure).

These structures (object relatives, object questions and object topicalization) are gradually acquired between the ages of 4 and 6 years and are typically mastered by Hebrew-speaking children with normal language acquisition around the age of 6 years (Friedmann and Lavi, 2006; Friedmann and Szterman, 2006; Friedmann et al., 2009, 2011; Friedmann and Costa, 2010).

Subject relatives (right-branching) and subject questions pose fewer comprehension difficulties to children with syntactic SLI compared to object relatives and object questions (Stavrakaki, 2001; Friedmann and Novogrodsky, 2003, 2004; Deevy and Leonard, 2004), although they are derived by phrasal movement. These structures are easier because the order of the agent and theme in them is canonical (Grodzinsky, 1990) and because they do not include crossing of the object over the subject (Friedmann et al., 2009). They are acquired earlier in typical development, and Hebrew-speaking children usually master them before the age of...
5 years. Given that structures with syntactic movement form a sensitive marker for syntactic SLI, and given that at least some of these structures are already acquired at the age of five, we used them for the diagnosis of the syntactic abilities of the children with thiamine deficiency in this study.

Thus, to assess syntactic abilities and lexical retrieval and to compare them to non-linguistic, conceptual abilities, we administered seven experiments using tests that were found to be sensitive to syntactic impairment, lexical retrieval impairment and conceptual deficits in Hebrew.

Materials and methods

Participants

The thiamine-deficient participants were 59 children (39 male and 20 female) aged 5.0–7.0 years [mean = 5.10 years, standard deviation (SD) = 0.5]. The children were members of Maccabi Health Services (the second largest healthcare service organization in Israel, which covers 24% of the Israeli population) that met the predetermined inclusion criteria: lack of neurological symptoms and lack of other possible sources for language impairment. The participants were not selected on their language profile but according to strict inclusion criteria: children who were fed the thiamine-deficient formula for at least 1 month (so the thiamine storage is expected to be exhausted), starting before the age of 13 months and who were considered neurologically ‘asymptomatic’ and had not displayed any neurological symptoms while being fed the thiamine-deficient formula and at the time the thiamine deficiency was discovered.

To be more confident that we measured deficits related to the infants’ nutrition, we excluded children who were born pre-term, had low birth weight, birth complications or other known neurological or genetic disorders. Hearing was screened, and all had normal hearing (10 children from the larger group of children with thiamine deficiency, who also demonstrated other neurological symptoms, had sensorineural hearing loss, so they were not included in the study). The sample did not include children whose mothers had a history of drug or alcohol abuse during pregnancy.

Procedure for identifying and screening the participants

Our participants were recruited from two sources with the same inclusion and exclusion criteria. When the absence of thiamine in the milk substitute formula was revealed, phone-based screening with medical and functional information was carried out by nurses of Maccabi Health Services across the country. Preliminary information identified 189 infants who might have been exposed to the thiamine-deficient formula to some extent—150 questionnaires were completed in full by parents. These questionnaires included detailed information on infants’ milk consumption (type of milk substitute, breast feeding) as well as developmental milestones and medical history. Of these 150, only 95 children met the inclusion and exclusion criteria reported above (35 infants did not consume the deficient formula at all, eight infants consumed it for <1 month, seven infants consumed the formula before it was thiamine deficient, three had low birth weight and two infants were >2 years old when they consumed the formula). We administered language assessments to 59 of these 95 children. Thirty-four of them arrived following the questionnaire, and 25 later participated in the study when they arrived as part of their follow-up in the hospital clinics, as reported below; of the remaining 36 children, the parents of 10 children chose not to participate in the study (parents of at least four of these children stated that they did not want to participate because the children were already being treated by a speech–language clinician), eight did not attend because of technical reasons (lived far away) and 18 could not be located due to changes in address or telephone number. Two additional children of the 34 were excluded from the research group because during testing they were diagnosed as suffering from cerebral palsy or autistic spectrum disorder. The other 27 participants were referred from outpatient clinics in the hospital, where they were followed as high-risk children due to consuming the thiamine-deficient formula (25 of them were also members of Maccabi Health Services). These children were enrolled in our study according to the strict inclusion and exclusion criteria previously defined.

Thus, our thiamine-deficient group included children who had not been selected according to their language profiles, but rather were included according to strict inclusion and exclusion criteria applied to make sure that they were indeed subject to thiamine-deficiency, and did not have any other medical background that could explain a language disorder. We did not assess IQ, but tested non-verbal conceptual ability using tests that correlate with IQ tests, in which almost all of the participants performed normally (Experiment 7). In addition, two other studies that assessed the IQ of a group of these children 2 years before and 2 years after the current study indicated that they had normal non-verbal IQ. Fattal-Valevski et al. (2009a) assessed the cognitive development of 20 of these children when they were 2–3 years old, using the Bayley Scales of Infant Development (Bayley, 1993), and found that their performance did not differ from their age- and gender-matched controls after controlling for the language factor. A recent study of 30 of these children when they were 2 years older than their age in the current study used the Raven Matrices test (Raven, 1965) and found that 29 of the 30 had normal or above normal performance in the Raven Matrices (z-scores between −1.11 and +2.57, with mean = +0.67), and one child (Z.A.) performed 1.84 SDs below the average for his age (Fisch et al., 2011). In addition, all of the children attended classes for children with normal IQ, and none of them attended intellectual disability classes. Background information on each of these 59 participants is presented in the online Supplementary material.

The control group included 35 healthy children (19 males) aged 5.2–6.6 years (mean = 5.10 years, SD = 0.4), age matched with the experimental group, and were recruited from the same local Family Health Care Units of the experimental group, serving the same communities. Gender distribution in the two groups did not differ significantly, \( \chi^2 = 1.3, P = 0.25 \), and the groups did not differ in birth weight, \( t(88) = 1.40, P = 0.17 \).

The children in the control group were fed with other milk sources, either dairy or non-dairy, and reported no developmental difficulties. Their hearing was screened and found to be unimpaired. Following language testing (Experiments 1–7), it turned out that three of the children in the control group performed as outliers on at least three language or conceptual measures (according to the Crawford and Howell’s t-test, Crawford and Howell, 1998). All three had syntactic impairment, and one of them also had a deficit in lexical retrieval. Their profile will be described in the concluding experimental section in the presentation of rates of specific language impairment in the normal and thiamine-deficient populations. For the comparison of each participant in the thiamine-deficiency group to the healthy control group (using the Crawford and Howell’s t-test), these three impaired children were excluded. (We also ran all the analyses with the control group including these three children, and there was no difference in the impairment classification of any of the thiamine-deficient participants.)
General method of assessment
Each child was tested individually in a single session that lasted 60–75 min. All the testing of the thiamine deficient and control children was carried out by the same experienced speech and language pathologist (I.F.). Participants were told that whenever they needed a break they could ask for it. Each meeting started with a short casual conversation with the participant and then the tests were administered. Parents (usually one of them) were present in the room filling out a questionnaire regarding demographic details, medical history and the child’s language and communication development and present performance. The parents of all participants in the thiamine deficient and the control groups provided informed consent for their children’s participation in the study, which was approved by the Institutional Ethics Review Committee.

During sessions, every response that differed from the target was written in detail by the experimenter, and correct responses were scored as correct. In addition, all sessions were audio-recorded and then transcribed in full after each session. Tests were administered in the same order to all children. No time limit was set in any of the experiments, and the experimenter repeated every item as many times as the participant requested. No response-contingent feedback was given, only general encouragement.

Statistical analyses
The performance of the thiamine-deficient group was compared with the performance of the control group using the maximum likelihood estimation (Poisson loglinear models algorithm). To compare the performance of each of the experimental participants with the performance of the normative healthy control group, we used Crawford and Howell’s (1998) t-test (see also Crawford and Garthwaite, 2002). This test is a modification to the independent samples t-test that can be used to compare an individual, treated as a sample of n = 1, with a sample, in a way that the single participant does not contribute to the estimate of the within-group variance. The comparison of the proportions of individuals in the two groups who performed at a certain level was carried out with Fisher’s exact test or a chi-squared test (according to the expected number of items per cell). The comparison of performance of each participant to chance level, i.e. to a guessing pattern, was performed using the binomial distribution. An alpha level of 0.05 was used for all comparisons.

Experimental investigation
The study included seven experiments that assessed the syntactic, lexical retrieval and conceptual abilities of the participants. Three experiments assessed the comprehension and production of relative clauses and of other complex syntactic structures that are known to be difficult for children with syntactic SLI using tasks sensitive to syntactic impairment in Hebrew-speaking children. Experiment 1 used a sentence–picture-matching task to evaluate the comprehension of subject and object relative clauses; Experiment 2 assessed the participants’ ability to produce relative clauses with a preference task; Experiment 3 compared the participants’ ability to repeat sentences of various complex syntactic structures including movements with a phrase, movement of a verb and embedding. The next two experiments tested the lexical abilities of the participants. Experiment 4 assessed the lexical retrieval abilities of the participants by testing naming of coloured pictures. Experiment 5 analysed lexical errors in a repetition task of simple sentences. Two additional tests assessed the participants’ conceptual ability: Experiment 6 assessed the ability to identify semantic associations through pictures, and Experiment 7 tested the ability to detect anomalies in pictures of events.

Syntactic abilities

Experiment 1: syntax–comprehension of relative clauses in a sentence–picture-matching task

Procedure
The participants’ comprehension of relative clauses was assessed using a binary sentence–picture-matching task (BAMBI, Friedmann and Novogrodsky, 2002), which was efficient in detecting syntactic SLI in Hebrew-speaking children (Friedmann and Novogrodsky, 2004, 2007, 2011) as well as syntactic difficulties in Hebrew-speaking individuals with agrammatism (Friedmann and Shapiro, 2003) and hearing impairment (Friedmann and Szterman, 2006, 2011; Friedmann et al., 2010a). The participant heard a sentence read by a native Hebrew speaker and saw two pictures on the same page, one above the other; one picture matched the sentence, and in the other picture the roles of the figures were reversed (Fig. 1). The participant was asked to point to the picture that correctly described the sentence.

Material
A total of 60 Hebrew sentences were tested for each participant. These sentences included 20 simple sentences, 20 subject relatives and 20 object relatives; see examples (4–6) for sentences that appeared with the picture pair in Fig. 1 (hyphenated words in the Hebrew examples represent words that are combinations of several words). All verbs were agentive transitives. All sentences were semantically reversible so that comprehension of the meaning of the words alone cannot determine the meaning of the sentence (namely, we did not use irreversible sentences like ‘The girl is eating ice cream’, only semantically reversible ones like ‘The girl is kissing the grandmother’). In each picture, the figures were of the same gender (a female nurse and a female soldier, a little boy and a grandfather, a giraffe, which is female in Hebrew, and a female cow, etc.), in order to preclude an agreement cue on the verb, as verbs in Hebrew agree with the subject in gender, number and person.

(4) Simple sentence
Ha-isha mecayeret et ha-yalda.
*The woman draws the girl.*

(5) Subject relative
Tar’e li et ha-isha she-mecayeret et ha-yalda.
*Show me the woman that draws the girl.*

(6) Object relative
Tar’e li et ha-yalda she-ha-isha mecayeret.
*Show me the girl that the woman draws.*
Sentences were randomly ordered. The participant saw 20 picture pairs three times; each picture pair appeared with all three sentence types. The correct picture in each pair was randomized (the matching picture in each pair was sometimes the top picture, and sometimes the bottom picture).

**Results**

The thiamine-deficient children showed severe difficulty in the comprehension of relative clauses (Fig. 2). Their performance in the comprehension of object relatives, a sensitive marker of syntactic SLI, was considerably poorer (62.4% correct) than that of the participants in the control group (78.1%), maximum likelihood $\chi^2(1) = 14.85, P < 0.001$. They showed difficulties even in structures that typically developing children already master at this age; the control children already performed at ceiling on the simple sentences, which do not include syntactic movement (99.7%), and on the subject relative sentences, in which the canonical order of thematic roles is preserved (99.5%). The thiamine-deficient children, in contrast, had difficulties even in these structures and performed 93.4% correct on the simple sentences and 92.5% correct on the subject relatives. The groups did not differ significantly on the groups level on either the simple sentences, maximum likelihood $\chi^2(1) = 1.71, P = 0.19$, or the subject relatives, maximum likelihood $\chi^2(1) = 2.12, P = 0.15$. There were, however, differences on the individual participant level.

The analysis of the performance of each of the participants in the thiamine-deficient group indicates that 28 of the 59 thiamine-deficient children performed significantly worse than the control group on the simple sentences, 29 performed worse than the control group on the subject relatives and 21 performed worse than the control group on the object relatives.

The comparison of the performance of each participant to chance level (using the binomial distribution), which indicates whether the children understood the sentences or were randomly pointing to one of the two pictures, also indicated a difference between the thiamine-deficient children and the control group. Whereas 42 of the thiamine-deficient children showed a guessing pattern, namely, performed at chance level on the object relatives...
(71% of the children), only 10 of the control participants performed at chance on these sentences (31% of the children); the rate of children who performed at chance was significantly larger in the thiamine-deficient group, $\chi^2 = 16.14, P < 0.0001$. In the simple sentences and subject relatives, all control participants performed above chance, but even in these relatively simple sentences, four and three children in the thiamine-deficient group, respectively, performed at chance level. Interestingly, two of the three children who performed at chance level on both the simple sentences and the subject relatives were also found in Experiments 6 and 7 to be conceptually impaired, which can explain their failure even with the simple sentences.

**Experiment 2: syntax–production of relative clauses**

Experiment 2 tested the ability of children with thiamine deficiency to produce relative clauses, in light of their marked inability to understand such sentences, which was observed in Experiment 1. In this experiment, relative clauses were elicited using a preference task (binary sentence–picture-matching BAMBI ADIF, Friedmann and Szterman, 2006; Novogrodsky and Friedmann, 2006). The children were presented with a short story about two figures and were required to choose which of the figures they preferred to be. The task was constructed in such a way that the choice would have to be formed as a relative clause. There were 20 short stories per participant, 10 eliciting subject relatives and 10 eliciting object relatives. The order of the subject and object relative target sentences was randomized.

The questions that elicited subject relatives described two children (two boys for a male participant, two girls for a female participant) performing two actions (Sentence 7); the questions that elicited object relatives described two children who are the themes of an action performed by two different agents (Sentence 8) or two actions performed by the same agent.

(7) Elicitation of subject relative:
There are two children. One child gives a present, and one child receives a present. Which child would you rather be? Start with ‘I would rather be . . . ’ or ‘The child . . . ’
Target answer: (Hayiti ma’adif lihiot) ha-yeled she-mekabel matana.
‘(I would rather be) the child who receives a present’.

(8) Elicitation of object relative:
There are two children. The father wakes up one child, and the alarm clock wakes up one child. Which child would you rather be? Start with ‘I would rather be . . . ’ or ‘The child . . . ’
Target answer: (Hayiti ma’adif lihiot) ha-yeled she-aba me’ir.
‘(I would rather be) the child who the father wakes up’.

Because of the large variability in the production of relative clauses in this age range, we tested a larger control group, which included 51 participants aged 4.10–6.3 years (mean = 5.8 years, SD = 0.5; 22 female). Three children in the thiamine-deficient group refused to participate in this task, so the data are given for 56 of the participants.

This task was found to reliably elicit relative clauses in Hebrew. Indeed, in Danish, Dutch, Austrian German and German, European Portuguese and Romanian this task, when run with 5 year-old children, gives rise to subject relatives with a passive verb instead of an object relative (Friedmann et al., 2010b). However, in Hebrew, which has a different structure, it does not give rise to passives at any age, only to relative clauses with active verbs. Moreover, even in Italian, where adults produce 88% subject relatives with passives in this task, young children do not produce passives—up to the age of 5 years not a single passive was produced in this task, and at the age of 5 years, the same age, we tested in the current study, still only few (around 10%) subject relatives with passives were produced, mainly ‘si fa’ and copular passives (Belletti and Contemori, 2010; Belletti and Rizzi, 2010; Belletti, 2011).

**Results**

The children with thiamine deficiency had significant difficulties producing both types of relative clauses. As shown in Table 1, in many cases they refrained from producing them by producing simpler structures or ungrammatical sentences. The differences between the thiamine-deficient group and the control group reflected both in the total number of correct productions of the target relative clauses (Fig. 2) and in the patterns of responses when they found it difficult to produce a relative clause.

**Subject relatives: correct productions and erroneous responses**
The control participants already mastered the production of subject relatives and produced them almost flawlessly and without difficulty (94.3% correct, SD = 8.8%), with only seven of the 51 control participants performing below 90% correct (producing

<table>
<thead>
<tr>
<th>Target structure</th>
<th>Response type</th>
<th>Thiamine deficient (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject relative</td>
<td>Correct subject relative</td>
<td>62</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Simple sentence</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fragment</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Embedded non-relative</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>“Don’t know” response</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Object relative</td>
<td>Correct object relative</td>
<td>24</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Subject relative instead of object relative</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Simple root clause</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Fragment</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Embedded non-relative</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>“Don’t know” response</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1 The distribution of responses in the relative clause elicitation task (average % out of all responses)

The participants in both groups also produced resumptive pronouns and filled gap relative clauses in response to the object relative elicitation task. These two response types can only be produced when an object relative is produced, so their analysis had to be out of the object relatives produced rather than out of the responses. The two groups produced the same rate of resumptive pronouns and filled gaps out of the number of object relatives they produced.
more than one incorrect response). In marked contrast, the thiamine-deficient participants found it very difficult to produce even subject relatives and produced only 62.3% correct subject relatives (SD = 37.5%), significantly poorer than the control group, with thiamine deficiency, 34 children performed below 90% correct, significantly more children than in the control group, \( \chi^2 = 24.93, P < 0.0001 \). The comparison of each participant to the control group indicated that 27 thiamine-deficient participants produced significantly fewer subject relatives than the control group.

The children with thiamine-deficiency adopted two main response strategies to avoid the production of subject relatives (Table 1). They produced non-relative rather than relative clauses, which were either simple sentences, single word fragments (a noun or verb) or sentences with embedding without a relative clause. Crucially, in the control group, all these responses amounted to only 2% of the responses. The other response that occurred for the thiamine-deficient children and not for the control participants was a ‘don’t know’ response. Interestingly, none of the groups omitted the embedding marker, indicating that the difficulty lies in the syntactic movement rather than in the embedding that exists in relative clauses (see the repetition task in Experiment 3 for further findings supporting this conclusion).

**Object relatives: correct productions and erroneous responses**

Although object relative clauses are still in the process of acquisition at the ages tested, there was also a clear difference between the thiamine-deficient group and the control group with respect to their ability to produce object relatives. The control participants produced 59% of the object relatives correctly (SD = 31.9%), whereas the children with thiamine deficiency produced less than half of the object relatives the control group produced—the thiamine-deficient children produced only 23.9% correct object relatives (SD = 27.4%; Table 1). This difference between the groups was significant, maximum likelihood \( \chi^2(1) = 82.36, P < 0.001 \). Seventeen of the 56 thiamine-deficient children could not produce even a single object relative, whereas only two of the 51 children in the control group did not produce any object relative (significantly more children did not produce an object relative in the thiamine-deficient group than in the control group, Fisher’s \( P = 0.0003 \)). Thirty-one thiamine-deficient participants produced significantly fewer object relatives than the control group.

The thiamine-deficient children produced a subject relative instead of an object relative more often than the control group, and many of these subject relatives were ungrammatical. When they produced a subject relative instead of an object relative, they either changed the head of the relative clause (for example, instead of saying ‘I would rather be the bell that wakes-up’, saying ‘I would rather be the bell that wakes-up the boy’), or changed the predicate in the embedded clause (‘I would rather be the boy that keeps on sleeping’).

Similarly to what we found in the subject relative targets, the thiamine-deficient children produced many simple sentences, sentence fragments and sentences with embedded clauses without a relative clause, instead of the target object relatives (Table 1). These kinds of responses were produced by both groups but significantly more often in the thiamine-deficient group, \( \chi^2 = 66.79, P < 0.0001 \). A response type that occurred only in the thiamine-deficient group was the ‘don’t know’ response, which accounted for 6% of their responses, but did not occur in the control group at all. In object relatives, like in subject relatives, none of the children in the two groups omitted the embedding marker.

**Experiment 3: syntax-repetition of structures with and without syntactic movement**

Experiment 3 further tested the syntactic abilities of the thiamine-deficient children using a sentence repetition task. The task enables full control of target sentences, and suggests a simple way to examine syntactic ability in different structures using the same task. Repeating a sentence in one’s native language is not a passive phonological copy of the input sentence. Rather, it involves comprehension and production and therefore difficulties in the comprehension and production of a syntactic structure are manifested in difficulties in repeating this structure (Lust et al. 1998; Friedmann and Lavi, 2006; Friedmann, 2007). Specifically, when we compare similar sentences (same length and words) that differ only in the relevant syntactic feature, if a participant succeeds in repeating one structure but fails in the other structure this might indicate a specific difficulty with the tested structure. Consistent occurrence of structural errors in the repetition of a certain structure by a child (and good repetition of the control sentence) can thus indicate a deficit in this specific structure, or that this structure has not yet been mastered.

We used the repetition task to examine how the thiamine-deficient children understand and produce syntactic structures that are known to be difficult for Hebrew-speaking children with syntactic SLI and children with hearing impairment. One such group of complex syntactic structures that are known to be impaired in these populations are sentences with Wh-movement (Friedmann and Novogrodsky, 2004, 2007, 2011; Friedmann and Szterman, 2006, 2011). We tested the repetition of object relatives, which include both Wh-movement and embedding, and of Wh questions and topicalization sentences, which include Wh-movement but no embedding.

We also tested other complex syntactic structures. These included sentences with embedded clauses without movement (such as ‘The boy said that the plate broke’). Whereas some studies indicated difficulty with such embedded structures in children with SLI (Leonard, 1995; Håkansson and Hansson, 2000; Schuele and Nicholls, 2000; Schuele and Tolbert, 2001; Schuele and Dykes, 2005), other studies reported that this type of structure is not impaired in syntactic SLI (Friedmann and Novogrodsky, 2007; see also Hamann et al. 2007; Delage and Tuller, 2010 for a matrix of complexity of different types of embedded clauses).

Two additional structures in the repetition task were sentences with other types of syntactic movement: sentences with verb movement to the second position in the sentence (after a temporal adverb and before the subject, see Table 2) and sentences with short movement from object to subject position.
A-movement, deriving the sentence ‘The leaf fell’ from the basic order ‘fell the leaf’). Simple control sentences without movement and without embedding were also included.

**Procedure**

The experimenter said a sentence and the participant was asked to repeat the sentence immediately, as accurately as possible. In the analysis of errors, structural errors were scored separately from lexical errors that did not affect the structure of the sentence.

**Material**

The test included 70 sentences: object relatives and object topicalization sentences, subject and object ‘which’ questions, sentences with verb movement, sentences with A-movement, sentences with embedded sentential complement and simple sentences without Wh-movement (Table 2). All sentences contained four words (accusative markers, embedding markers and prepositions were counted with the word following them). All the sentences derived by Wh-movement were semantically reversible. Half of the verbs in the simple sentences and the sentences with verb movement were transitive and half were intransitive verbs. The sentences with embedded clauses included an embedded intransitive verb.

**Results**

The results of the repetition experiment joined the two previous syntactic experiments in showing a marked syntactic deficit in the thiamine-deficient group. The results clearly indicated that the thiamine-deficient children found it very difficult to repeat syntactically complex structures, although most of the children were able to flawlessly repeat simple sentences and sentences with embedded clauses. Table 2 reports the rate of sentences of each type that the participants were able to repeat without structural errors (lexical substitutions were not coded as errors in this analysis). The results indicate difficulties in object relatives, topicalization structures and object questions, which were repeated at a level significantly poorer than the control group. As shown in Table 2, both groups experienced difficulty in the verb movement structures, but the difference between the groups was still significant. The thiamine-deficient group performed significantly worse than the control group on this structure too.

The analysis for each individual with thiamine deficiency in the structures with Wh-movement (object relatives, object questions and topicalization) and the structures with verb movement (Table 2) indicate that more than a third of the children with thiamine deficiency, and in some structures more than a half of these children, performed significantly below the control level on Wh-movement structures.

The test also shows that not all types of sentences are difficult for children with thiamine deficiency. As shown in Table 2, their repetition of simple sentences and of sentences with embedded clauses, as well as their repetition of sentences with A-movement was good and similar to the control group. The good performance in these structures can be seen both in the high percentage of correct repetition at the group level and in the very small number of participants who performed worse than the control group. Good performance on some of the structures is a crucial finding for our understanding of the deficit; this shows that the deficit of
the thiamine-deficient children is not a general inability to repeat sentences. The failure in repetition is constrained by syntactic lines, and indicates a selective syntactic deficit, which resembles the pattern known from syntactic SLI.

Figure 2 presents the two sentence types that were difficult for the thiamine-deficient group to repeat: object Wh-movement (including topicalization, object relatives and object questions) and verb movement.

**Error analysis**

In the analysis of the errors in repetition, we distinguished between **structural errors**, in which the child changed the structure of the sentence, reversed the thematic roles in it, or produced it ungrammatically, and **lexical errors**, in which a noun was substituted with another that did not appear in the target sentence (policeman → neighbour), a verb was substituted with another having the same argument structure (like → love) or an omission, substitution or addition of a temporal phrase (yesterday → tomorrow). Some lexical substitutions were indicative of a problem with the thematic roles of the sentence and were hence counted as structural errors (these included reversals and doubling of the noun phrases in the sentence, described below).

**Structural errors**

The most common errors that occurred in the repetition of object questions, object relatives and topicalization, i.e. all the structures in which the object moved across the subject and in the verb movement sentences, were change of syntactic structure of the target sentence to a structure that was syntactically simpler (‘This is the clown that the kindergarten teacher pushed’ → ‘This kindergarten teacher pushed the clown’), word order errors (‘Yesterday slept mommy in bed’ → ‘Yesterday mommy slept in bed’), reversals of the participants in the sentence (‘This is the girl that grandma drew’ → ‘This is the grandma that the girl drew’) and substitutions of one of the two noun phrases in the sentence with the other noun phrase in the same sentence, resulting in doubling of one of the noun phrases (‘This is the girl that grandma drew’ → ‘This is the grandma that grandma drew’). Reversal and doubling errors can be explained in that when the syntactically impaired children heard these sentences, they failed to understand ‘who did what to whom’ in the sentence, namely, they failed to assign the thematic roles in the sentence. As a result, when repeating the sentence, they sometimes switched the agent and the theme. This created sentences in which one of the arguments acted as both the agent and the theme, or sentences with a complete reversal of the roles.

Another indication of the same difficulty with thematic roles could be seen in the omission of the accusative case marker. In the repetition of object topicalization and object questions, many errors involved the omission of the accusative marker. In Hebrew, accusative markers (‘et’) appear with the (definite) object (Shlonsky, 1997; Danon, 2001, 2006; Ruigendijk and Friedmann, 2008), which, in the sentences that we used, always had the role of the theme. If a child cannot identify the thematic roles in a movement-derived sentence, they will also not know to which of the arguments the accusative marker should be attached, and as a result would not be able to produce the accusative marker with the theme (the object). Hence, thematic role difficulties can be reflected in accusative marker errors. Crucially, the omission of the accusative marker does not result from a deficit in the case system, as indicated by the finding that the accusative marker was never omitted in simple sentence or in sentences with an embedded clause that did not involve movement.

**The relation between lexical errors and syntactic ability**

The analysis of the lexical errors raised an interesting finding: the difficulty in the sentences derived by syntactic movement was expressed not only in the production of structural errors but also, the increased syntactic difficulty yielded more lexical errors. This was true even when we did not include lexical errors of reversal and doubling in the analysis. The children with thiamine deficiency produced significantly more lexical errors in the sentences derived by Wh-movement (15.6% lexical errors in object relatives, topicalization and object questions) than in the sentences without Wh-movement (6.8% lexical errors in simple sentences, sentences with embedded clauses and sentences with unaccusative verbs, with no significant difference between these three simpler structures), $\chi^2 = 62.59, P < 0.0001$.

Within the thiamine-deficiency group, the children who had difficulty in the comprehension and production of Wh-movement (who performed worse than the control group on at least two syntactic measures) produced significantly more lexical errors in repeating sentences with object Wh-movement than the children whose syntax was unimpaired. This analysis indicated that 97% of the lexical errors that were produced in the sentences with the object Wh-movement (object questions, object relatives and topicalization) were produced by the children with the syntactic difficulty. The nine children who were unimpaired syntactically produced an average of 3% lexical errors on object Wh-movement sentences (less than a single lexical error on the average), whereas the children who were syntactically impaired produced an average of 18% lexical errors on these structures. This formed a significant difference, $\chi^2 = 22.31, P < 0.0001$.

Along similar lines, 21 of the children with thiamine deficiency made many (>30%) structural errors in the repetition of sentences with object Wh-movement. All of them also made 12% or more lexical errors in these structures. Importantly, nine children produced lexical errors only or almost only on these movement structures, but did not produce lexical errors (<5%) in the simple or embedded structures, indicating that the source of their lexical errors in repetition was their syntactic difficulties, rather than lexical retrieval deficits.

Thus, the three experiments evaluating the syntactic abilities of the thiamine-deficient participants indicated that these children had a marked deficit in the comprehension of relative clauses, especially in object relatives, and in the production of both subject and object relatives. Their difficulty in object relatives was also evinced in their inability to repeat these sentences. They also showed a marked difficulty in repeating other sentences with a similar structure: object topicalization sentences and object questions. They were, however, able to produce sentences with other kinds of syntactic complexity, such as sentences with embedded clauses.
Lexical abilities

**Experiment 4: lexical retrieval–picture-naming test**

Experiment 4 tested the lexical abilities of the thiamine-deficient children using the classic test of picture naming. This test included 50 coloured photos (the pictures were taken from the Tavor test for Hebrew vocabulary, 2007). The target naming responses were of various syntactic and semantic categories: 23 concrete objects (tree, curtain) and object parts (wings), five pictures of several items for which the participant was requested to provide the superordinate categories (vehicles), 13 verbs inflected for gender and number, seven adjectives inflected for gender and number, and two pictures that were combined with a question that elicited an adverb or an inflected preposition ('before-him'). The target words included morphologically complex words, in various derivational noun, verb and adjectival templates. They included masculine and feminine nouns, verbs and adjectives.

Each response was scored as correct or incorrect. We scored a response as correct if it was an existing word in Hebrew that correctly described the picture, and at least a third of the children in the control group used it in response to this specific picture. We also analysed the types of errors and non-target responses that the children produced when they failed to name the picture.

**Procedure**

Each picture was presented on a separate page. For each picture, the experimenter asked a lead-in question (such as ‘What is this?’ or ‘What do the girls do here?’) in order to direct the participants to the target answer (noun, verb, category, morphological inflection etc.)

**Results**

The results of the naming task, summarized in Fig. 3, indicate that the lexical retrieval domain was also impaired in the thiamine-deficient group. The children with thiamine deficiency produced significantly fewer correct answers (mean = 77.2%, SD = 13.5%) than the control participants (mean = 93.4%; SD = 2.2%), maximum likelihood $\chi^2(1) = 32.23$, $P < 0.001$. The analysis of the performance of each of the participants in the thiamine-deficient group indicated that 37 thiamine-deficient children performed significantly worse than the control group on the picture-naming test. When considering correct immediate response (namely, not including self corrections and correct responses after long delays), which is the way naming is often evaluated (Howard et al., 1985; Nickels and Howard, 1995; Best et al., 2002), the picture is even more severe—52 thiamine-deficient children performed significantly worse than the control group ($P < 0.04$), and only seven of them performed within the normal range. The control group provided correct first responses for 43.8 of the 50 target items (87.6%, SD = 2.60), whereas the children with thiamine deficiency provided only 34.4 correct first responses on the average (68.8%, SD = 6.69). This formed a significant difference between the groups, maximum likelihood $\chi^2(1) = 47.80$, $P < 0.001$.

An important result emerges from the comparison of correct naming at first response and correct naming at final response. In the final response, after hesitations and incorrect responses, 56 of the 59 participants were able to retrieve correct names they had been unable to retrieve on the first response. This included 51 of the 52 participants whose first naming was significantly poorer than that of the control participants. As we saw above, 15 of them even reached the normal naming level in final response. This finding suggests that their lexical impairment does not result from restricted vocabulary. Rather, the words exist in their lexicons, but the retrieval from the lexicons or the activation of the entries in the lexicon is impaired. This suggests that it is the retrieval mechanism (in this case, the establishment of the cascaded mechanism for lexical retrieval; Nickels, 1997; Nickels and Howard, 2000) that is impaired for these children.

The conclusion that the deficit is in lexical retrieval rather than in lexical knowledge is also supported by the finding that 20 of the children were given phonological cues when they failed to name, and all of them benefited from this cue and were then able to retrieve correct names they had been unable to retrieve previously (correct naming following a cue was not counted as a correct response in the above analysis, but it served to stop latent search for the word and to reduce frustration).

The children with thiamine deficiency made predominantly semantic errors, including substitutions with a word from the same semantic category ('chair' for a picture of a table), associations ('napkins' for a table), words from a higher order category ('furniture' for table), naming of another aspect or item in the picture (despite specific pointing and a lead-in question) or definitions of the target word. The thiamine-deficient children produced significantly more semantic errors (9.4 of the 50 responses, 18.8%) than did the control participants (only 4.0, 8%), maximum likelihood $\chi^2(1) = 87.37$, $P < 0.001$.

Another response that occurred significantly more often in the thiamine-deficient group was the ‘don’t know’ response. The
children with thiamine deficiency produced 2.14 such responses on the average, compared with only 0.69 in the control group. The thiamine-deficient group produced significantly more ‘don’t know’ responses than the control group, maximum likelihood $\chi^2(1) = 30.76, P < 0.001$. The difficulty in lexical retrieval was also manifested in the rate of hesitations and responses given after long latencies (>5 s), which occurred significantly more frequently in the thiamine-deficient group. The children with thiamine deficiency had an average of 1.45 long hesitations in this task, whereas the control group had only 0.16 hesitations on the average, maximum likelihood $\chi^2(1) = 44.74, P < 0.001$.

An indication for the morpho-syntactic difficulty of the children with thiamine deficiency could be seen in this task too. Hebrew verbs inflect for person, gender, number and tense, and they are also part of a derivational template (binyan), which often determines semantic and syntactic properties of the verb (for example, for the root NSK, naSak and niSek are the transitive kiss, hitnaSek is the reciprocal kiss and nushak is the passive form of kiss). Many of the thiamine deficient children produced verbs in the wrong template. When analysing the inflection and derivation of the verbs and adjectives in the test, 29 of the children with thiamine deficiency made such errors (0.73 errors on the average for the whole group), whereas only two of the control participants made such errors (with an average of 0.09 errors for the group); this formed a significant difference between the groups, maximum likelihood $\chi^2(1) = 21.36, P < 0.001$. Because of the very scarce production of morphological errors in the control group, each of the 29 participants who produced even a single morphological error made more such errors than the control group.

In another analysis, we used the ‘language age’ norms of the Tavor test (the test from which we took the pictures for the naming test). This ‘language age’ is a measure of naming-performance age, i.e. the age of children who succeeded in as many items as the participant did. We compared the naming-performance age of the thiamine-deficiency group and the control group. This analysis indicated that the thiamine-deficient children performed in the Tavor test at an average level that is 20 months younger than the control group, maximum likelihood $\chi^2(1) = 44.74, P < 0.001$.

No significant differences were detected in the thiamine-deficient group between the naming of nouns, verbs and adjectives (with averages of 80, 85 and 81% correct, respectively). The retrieval of category names was very difficult for them, yielding a mere 51% correct, compared with 95% correct in the control group.

**Experiment 5: lexical retrieval–lexical errors in sentence repetition**

In Experiment 5, we assessed the children’s lexical ability through sentence repetition. We used the sentence repetition test reported in Experiment 3, but this time we analysed it for the number of word substitutions in repetition of the sentences that were not syntactically difficult for the children.

**Analysis**

To make sure that we counted lexical substitutions that result from lexical difficulties rather than from syntactic difficulties, we took two measures of precaution. First, we only analysed lexical substitutions in sentences without Wh-movement, namely, we excluded the 30 sentences that were found to be syntactically difficult for the participants, and only included simple sentences, sentences with embedded clauses without movement, and sentences with verb movement or short movement (A-movement). This was done because, as in Experiment 3, children with syntactic difficulties made more lexical errors in Wh-movement structures, as a result of the elevation of the repetition difficulty. The second precaution we took was not to include errors in which one word in the sentence was replaced with another word in the sentence (doubling or reversal errors such as repeating ‘The girl kissed grandma’ for a target ‘The grandma kissed the girl’), because such a substitution could result from a syntactic difficulty in thematic role errors, namely, in interpreting ‘who is doing what to whom’ in the sentence (as in Experiment 3). Also, we did not count the omission of function words (of the accusative marker or of prepositions) as lexical errors. This was a conservative count, which probably led to underestimation of the lexical difficulties in repetition of the participants with thiamine deficiency, but this was necessary to isolate the lexical component of the deficit.

**Material**

As described in Experiment 3, each child repeated 70 sentences, from which we analysed the 40 sentences without Wh-movement. Each sentence contained four content words and accusative markers, embedding markers and prepositions. The sentences with embedded clauses included two nouns and two verbs, and the rest (simple, A-movement, verb movement) included two nouns, one verb and one adverb. Thus, each child repeated 160 content words in this test, including 80 nouns, 50 verbs and 30 adverbs. All the nouns and verbs were words that are familiar to kindergarden children, with high frequency (mean = 305 occurrences per million for the nouns and mean = 562 occurrences per million for the verbs, frequency data from a Hebrew blog corpus encompassing 165 188 396 words in colloquial Hebrew (Linnen, 2009).

**Results**

The control participants made only 15 lexical errors in total in the repetition of all 5120 words in the sentences without Wh-movement. Namely, each control participant made less than half a lexical error on average in the whole task, repeating 40 sentences (160 words). The thiamine-deficient group, on the other hand, made 172 lexical errors in total in repeating these simple sentences, with some of the participants making up to 22 lexical errors in repeating these sentences, with an average of 3.0 errors per participant. (The analysis of lexical errors in all 70 sentences yielded similar results, the thiamine-deficiency group made an average of 8.0 lexical errors, the control group made 2.5 lexical errors, with a significant difference in the production of lexical errors between the groups, $t(89) = 3.61, P = 0.0003$.) The thiamine-deficient group made significantly more lexical errors in the repetition of sentences without Wh-movement than did the control group, maximum likelihood $\chi^2(1) = 75.26, P < 0.001$. 


This difference also manifested itself in the individual participant analysis—24 of the 59 children with thiamine deficiency made significantly more lexical errors than the control group even in this relatively simple task of repetition. All but two were children that showed lexical retrieval difficulties in the naming task (Experiment 4). (These two children were T and I. T was one of the children who made most lexical errors in the repetition of sentences with Wh-movement, possibly due to his very impaired syntax. In the repetition of the sentences without Wh-movement, he made four lexical errors, but these also seemed to be related to his syntactic impairment: he omitted three temporal adverbs, and changed one unaccusative verb into a transitive verb, yielding an ungrammatical sentence. I made only two lexical errors in the repetition of simple sentences, but two errors were already significantly more errors than the control participants produced.) Only three children in the control group made more than a single lexical error in the repetition of the 40 sentences. The rate of children who made more than a single lexical error in the thiamine-deficient group was significantly larger than this rate in the control group, Fisher's $P = 0.001$.

Of the 52 participants who performed below the controls in the lexical retrieval task (Experiment 4) as measured by correct first response, 22 also made significantly more lexical errors than the controls in sentence repetition. Taking the more lenient measure of correct naming at some point (even after an incorrect response or a long hesitation) of the 37 participants who had significantly poorer naming than the control group according to this measure, 19 participants also made more lexical errors in repetition than the control group.

Two twin girls, E.O. and E.D., who showed the same pattern of impairment, with intact syntactic abilities and impaired naming in Experiment 4, were found to be conceptually impaired (see Experiments 6 and 7 below). These girls did not make lexical errors in sentence repetition despite their very poor picture naming. This pattern may point to the functional source of the naming impairment of the two girls. It suggests that their naming deficit is located at a stage earlier than the phonological output lexicon, in the lexical-semantic stage (see Caramazza and Hillis, 1990; Butterworth, 1992; Caramazza, 1997; Hillis, 2001 for discussion of the lexical-semantic stage) or in the access to it from the conceptual or visual system. This allowed them to repeat words without errors, but hampered their picture naming.

Not everything is impaired: conceptual abilities

Experiments 6 and 7 tested the conceptual abilities of the thiamine-deficient participants. The participants’ performance in the previous tests already indicates that they did not suffer a general cognitive or conceptual impairment. First, most children demonstrated full cooperation and normal motivation throughout the long testing session, and showed good comprehension of the tasks and the task situation. These observations suggest that these children had a language deficit, rather than a more general cognitive one. Second, they showed good performance on some sentence structures, but not on others. For example, they performed relatively well on the comprehension of simple sentences that required the choice of one of two complex pictures, indicating that their poor performance on the comprehension of object relatives in the same task did not result from a difficulty in the comprehension of the task, the meaning of the words, or the pictures, but was rather related to their syntactic difficulty. Other indications for the preserved cognitive ability of the thiamine-deficient group, as reported in the participants’ description, come from the studies that were administered 2 years before and 2 years after the current study for many of the participants, which indicated preserved non-verbal cognitive ability in the Bayley and Raven tests (Fattal-Valevski et al., 2009a; Fisch et al., 2011).

**Experiment 6: conceptual ability-picture association task**

In Experiment 6, we tested the participants’ conceptual abilities using a picture association test (Biran and Friedmann, 2007). The test included 33 triads of pictures, in which a target picture was presented on top, with two additional pictures presented underneath it. The participant was requested to point to the picture that is more closely related to the target picture. The two bottom pictures were semantically and/or visually related to each other, but only one of them related conceptually to the target picture. For example, a picture of a soup bowl as a target picture and pictures of a spoon and a fork; a target picture of long hair (the head of a girl, shown from behind), with a comb and a toothbrush; or the triad shown in Fig. 4, a target picture of wool of a lion and a sheep.

The participants in this experiment were 51 thiamine-deficient children (this test was not administered to the first eight participants tested), and the 32 control participants without language impairment.

**Results**

The results showed that the large majority of children with thiamine deficiency performed very well on this task. Their average performance was 95.2% (SD = 7.6%), and the control group’s performance was 98.2% (SD = 1.7%).

The control participants made between 0–2 errors (31–33 correct), and so did most of the children with thiamine deficiency—42 of the 51 children performed well on this task and made 0–2 errors. Nine of the 51 thiamine-deficient children had more errors than the control range on this test, i.e. more than two errors (four children made three errors, two made four errors and three made more than four errors). There was no significant difference in the performance on the association task between the two groups, maximum likelihood $\chi^2(1) = 0.61$, $P = 0.44$.

Because the test required a selection between two options, a guessing pattern should have resulted in a chance performance distributing around 50% correct. A binomial distribution test indicated that there was only one thiamine-deficient child who performed at a guessing level in this test.

Thus, for a large majority of children with thiamine deficiency, the conceptual ability was unimpaired. Except for the twin sisters reported in Experiment 5, whose conceptual impairment led to
impaired picture naming, the other children with thiamine-deficiency showed poor performance in the language tests described in Experiments 1–5 in the absence of conceptual impairment. This indicates that their difficulties resulted from syntactic and/or lexical impairments rather than from conceptual impairment.

**Experiment 7: conceptual ability—detecting absurdities in pictures**

Another task we used to assess the conceptual ability of the participants was an absurdities test—a task that required detection of abnormalities in photos of daily events. The ability to detect absurd events is included in intelligence tests, for example the verbal reasoning part of the Wechsler Intelligence Scales for Children, as it is assumed to serve as a good indicator of conceptual ability and world knowledge. Absurdities detection and report were also found to correlate with the performance on Raven Matrices (Raven, 1965), which is taken to be a measure of non-verbal intelligence (Fattal, 2003).

The participants were presented with five coloured pictures of everyday events, each containing a different abnormality, such as a girl eating a sandwich with flowers inside, or an old man cutting slices of bread with scissors (ColorCards What’s Wrong, Speechmark Publishing). For each picture we asked the participant whether there was anything funny or weird in the picture, and if so, they were asked to describe what they found strange in the picture. Because we were interested in the conceptual, rather than language abilities of the participants in this test, we only coded whether or not the absurdity was detected and did not consider the linguistic aspects of the absurd description.

**Results**

The results of this test joined the results of Experiment 6 in indicating the participants’ good conceptual ability. No significant difference was found between the performance of the thiamine-deficient group (mean = 95.3%, SD = 11.9%) and that of the control group (mean = 96.9%, SD = 7.4%), maximum likelihood $\chi^2(1) = 0.04$, $P = 0.84$.

The children in the control group detected and described abnormalities in 4–5 of the five pictures, and so did most of the children with thiamine deficiency. Only three of the 59 children with thiamine deficiency performed below this range, finding only two or three of the abnormalities in the pictures (two of these children were also the children who were most impaired in the association test, and the third one did not participate in the association test).

Thus, although this test is able to identify conceptual difficulties, as indicated by the finding that three of the children had difficulties in it, and by previous studies that showed that adults who have conceptual impairment also make errors on the absurdities test (e.g. Shuttleworth and Huber, 1989; Rumsey and Hamburger, 1990), most of the children with thiamine-deficiency performed well on it.

Thus, this test, like the other conceptual test described in Experiment 6, demonstrates a conceptual ability that is for the most part preserved; it emphasizes that the deficit following thiamine deficiency is manifested mainly in syntactic and lexical abilities, i.e. in language abilities rather than general cognitive abilities.

**General results**

The general picture that emerged from the whole test battery, as summarized in Table 3, was that almost all children in the thiamine-deficiency group, who consumed a thiamine-deficient formula during their first year of life, had language impairment when they were 5–7 years of age. In the thiamine-deficient group, 57 of the 59 children had language impairments in the syntactic domain, in lexical retrieval, or in both. In contrast, the control group included only three children who failed on at least three measures across all domains tested together. All three had
Table 3 Individual profiles of the 59 children in the thiamine-deficient group in the syntactic, lexical and conceptual measures

<table>
<thead>
<tr>
<th>Participant</th>
<th>Syntactic tests</th>
<th>Lexical tests</th>
<th>Conceptual tests</th>
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S = a syntactic deficit (in two measures); L = a lexical retrieval deficit (in naming); C = a conceptual deficit (in either of the two measures); = child did not participate in this task.

*We considered AO syntactically unimpaired even though he performed significantly below the control group in two measures, because he only made one error each in the simple and subject relative conditions in the comprehension task, and the rest of his syntactic measures were very high.

Shaded cells with X indicate significantly impaired performance compared with the control group.
syntactic SLI, and one also showed a deficit in lexical retrieval. This figure corresponds with the rate of SLI in the general population, which is around 7–10%. The rate of children with language impairment in the thiamine-deficient group (97%) was significantly higher than in the control group (9%), Fisher’s $P < 0.0001$.

Notice that the difference between the groups could not be ascribed to different socio-economic status of the two groups, because the control children were selected from the same local Family Health Care Units as the children with thiamine deficiency, serving the same neighbourhoods and communities.

Whereas we did not test the entire cohort of children that were exposed to thiamine deficiency, and therefore, we cannot draw conclusions regarding the exact rate of language impairment in the population of children with thiamine deficiency, we can safely conclude that the prevalence of language impairment in this population is significantly higher than that of the typically developing population. One conjecture that this study raises is that it is possible that the language impairment of children who are currently diagnosed with SLI in the general population may actually be a result of thiamine deficiency in infancy or at least abnormal cerebral maturation of the type that is induced by thiamine deficiency.

Another important result of the look at the whole group and the whole test battery is that syntax and lexical retrieval were often both affected (in 42 of the participants, 71%), but double dissociations were detected, indicating that these abilities can be selectively affected by thiamine deficiency. In general, 80% of the children showed syntactic impairment (performed significantly below the control group in at least two syntactic measures), and 88% of the children were lexically impaired (as indicated by performance significantly poorer than the control on picture naming). There were five (8%) children who were impaired in syntax but not in lexical retrieval, and 10 (17%) who were impaired in lexical retrieval but not in syntax.

With respect to conceptual abilities, the picture is very different. Of the 59 children, only six showed impaired performance on at least one conceptual test (making $>3$ errors on the association task or $>1$ error in the absurdities task). The other 53 children (90%) demonstrated normal conceptual abilities. Further testing of these children when they are older will determine whether they catch up with the linguistic abilities of children their age, and will allow for the comparison of their impairment with that of children who are diagnosed with SLI that does not result from a (known) nutritional base.

Finally, an analysis of the results of the control group rules out a possible explanation according to which it was not the thiamine deficiency in the milk formula that caused the language impairment, but rather the fact that the formula was non-dairy. To examine this possibility, we compared, within the control group, children who consumed a non-dairy formula and children who consumed a dairy formula or were breast-fed. The results for each of the seven experiments were that the control children who consumed a dairy formula or were breast-fed did not differ from the control children who were fed with a dairy formula. The comparison of the syntactic experiments: object relative comprehension, relative clause production, and Wh-movement sentence repetition yielded no significant difference between these subgroups of the control group, $P > 0.20$. Similarly, the lexical tests and the conceptual tests showed no difference between the control subgroups, $P > 0.40$. Thus, clearly, the language impairment cannot be ascribed to the consumption of a non-dairy formula, and should be ascribed to the lack of thiamine in the formula.

### Discussion

Despite the high prevalence of language impairment, its biological bases are not completely understood. The literature of specific language impairment often seeks for genetic bases for this deficit (Bishop et al., 1995; van der Lely and Stollwerck, 1996; Bartlett et al., 2002; Bishop, 2003). The current study indicates another important source for language impairment, which has not been reported until now—a nutritional source. We reported on 59 children who, in their first year of life, consumed a thiamine-deficient milk substitute for at least 1 month. Because body storage of thiamine is minimal, when dietary intake does not fulfill the thiamine needs, stored thiamine can be used up in 2–3 weeks. Thus, these children were exposed to thiamine deficiency. Although the deficiency in the milk substitute was detected and the children were treated with thiamine, the vitamin deficiency for a certain critical period of time had long-lasting and serious effect on their language development. When they were 5- to 7-years old, 57 of these 59 children showed a marked language deficit in syntax, lexical retrieval or both.

Of the thiamine-deficient children, 80% showed marked syntactic difficulties. Their syntactic deficit was pronounced in the same way classic syntactic SLI is pronounced. In the comprehension task, they showed problems in the comprehension of relative clauses, especially in object relatives, sentences in which the object moves across the subject, but also in subject relatives, which are fully acquired by typically developing children at this age. In the production task they showed marked difficulties in the production of object relatives, but also in the production of subject relatives, which Hebrew-speaking children their age already produce effortlessly. The repetition task confirmed the marked difficulty in relative clauses—the children in the thiamine-deficient group found it difficult to even repeat short sentences with object relative clauses. The repetition task added two new aspects to the description of their syntactic difficulty. The children had difficulty not only in relative clauses but also in other sentence types that are derived by Wh-movement of the object across the subject: object Wh-questions and topicalized sentences. Another important finding of this task was that the children showed good performance on other types of sentences. Not only did they repeat simple sentences well, they could also repeat sentences with embedding without movement, indicating that their syntactic impairment does not span to all kinds of complex structures, but rather focuses on certain structures (those with syntactic movement); they could also repeat sentences with short syntactic movement (of the object to subject position, A-movement), again showing the selectivity of the deficit and the similarity of their pattern of impairment to syntactic SLI. Many of them also manifested a morpho-syntactic impairment in the naming task, in which they
produced verbs and adjectives in the wrong derivation or inflection.

Lexical retrieval was found to be impaired in 88% of the thiamine-deficient children. Their lexical retrieval difficulties were similar to the deficits shown by children with developmental anomia (lexical SLI). They showed hesitations, ‘don’t know’ responses, and semantic paraphasias. For many of the children with lexical retrieval difficulties, the deficit was even reflected in a difficulty to repeat words, substituting and omitting nouns, verbs and adjectives in the sentence repetition task.

Their lexical deficit was rooted in lexical retrieval rather than in the establishment of vocabulary. Almost all of the children who were unable to retrieve words at first response, and who made semantic errors, ‘don’t know’ responses, or long hesitations, were often able to retrieve the word after repeated attempts or after they were given a cue, indicating that these words were present in their lexicon, but they had difficulty in retrieving them from the lexicon.

A crucial result of the broad test battery used in the current study is that not everything is damaged by thiamine deficiency. First, conceptual ability was preserved for 90% of the children with thiamine deficiency. This is in marked contrast to the mere 3% of children who demonstrated intact language (syntactic and lexical) abilities. What does this say about the function of thiamine in the development of the brain during the first year of life? Several models are imaginable, each requiring a more direct assessment. One possibility is that the source of the difference between the language skills, which were impaired, and the conceptual skills, which were generally spared, lies in the difference in critical periods for the acquisition of language abilities and conceptual abilities. Namely, we know that for syntax of the first language acquired, there is a critical period, which occurs during the first year of life (Szterman and Friedman, 2003; Friedmann and Szterman, 2006; see also Calderon and Naidu, 1998; Yoshinaga-Itano and Apuzzo, 1998a, b; Yoshinaga-Itano, 2003 for studies that did not assess syntax directly but report results regarding early critical period for language and communication abilities in general, and Ruben, 1997 for different critical periods for different language domains; see Monjaux et al., 2005 for a discussion of critical period in children with epilepsy). It is possible that the development of conceptual ability is not subject to a similar critical period. Thus, for children who were thiamine deficient during the first year of life, it is possible that, whereas the critical period for syntax has passed and this damage is no longer repairable, the conceptual ability could develop at a later age. Another approach is that thiamine is involved in the development of neurotransmitters or other substances relevant for language areas but not for conceptual areas, or possibly that the lack of thiamine primarily affects certain brain systems that are related to language more severely than other areas that support the development of conceptual abilities.

Another point of selectivity relates to the language ability that was impaired. Some children demonstrated a selective deficit in syntax but not in lexical retrieval, and some children had a lexical retrieval deficit with unimpaired syntax, indicating that these language modules can be selectively impaired, and possibly that they follow separate developmental paths.

Selectivity was also witnessed within the syntactic domain. Whereas the thiamine-deficient children were very impaired in the comprehension, production and repetition of sentences derived by Wh-movement, they still produced sentences with short movement of the object to subject position (A-movement) normally. They also had good production of sentences with embedding. All but one child with thiamine deficiency repeated sentences with A-movement and sentences with embedding with at least 80% accuracy, and most of the children repeated these sentences at ceiling, even though they are syntactically complex.

One interesting result arises from the comparison of the effects of thiamine deficiency in adults and what we found here regarding its effect in young children. Thiamine deficiency in adults gives rise to Wernicke’s encephalopathy, which later, in the chronic stage, results in Korsakoff’s syndrome. As far as we know, there are no reports of syntactic or lexical retrieval impairments in Wernicke’s encephalopathy or in Korsakoff’s syndrome. Wernicke (1881) himself reported that his patients had ‘tired speech’ but did not report syntactic or naming impairments in the comprehension or production of adults with Wernicke’s encephalopathy. Individuals with Korsakoff’s syndrome have memory problems, including problems in the memory of words (for example, recalling which word was said to them in a memory task), but do not have lexical retrieval problems and perform well on the vocabulary part of the Wechsler Adult Intelligence Scale (Mair et al., 1979; Butters et al., 1980).

The handbook of neuropsychology even states that a good way to make a differential diagnosis between Alzheimer’s disease and Korsakoff’s syndrome is based on the observation that ‘Alzheimer, but not Korsakoff, patients tend to suffer from anosmia...’ (Delis and Kramer, 2000, p.26). An early study that focused carefully on language in patients with Korsakoff’s syndrome concluded that ‘grammar and syntax are formally correct and there is no real nominal aphasia’ (Clarke et al., 1958, p.193).

Whereas adults with thiamine deficiency usually do not display language impairments, the current study revealed that children who experienced thiamine deficiency during the first year of life do show language impairments. The central difference between children and adults who suffer thiamine malnutrition is the incomplete development of the child’s brain during exposure to the deficiency. This finding suggests that once language acquisition is completed, as in the adult brain, thiamine deficiency does not affect language areas or abilities. However, because thiamine also plays a central role in brain development, its absence during the development of brain substrates necessary for language development impairs syntax and lexical retrieval (see BA, 2005 for a detailed study of the different effects on the behaviour of rats following thiamine deficiency in different stages of development). Because a large proportion of the children who were exposed to a thiamine-deficient diet for at least a month during their first year displayed language impairments, we may conclude that thiamine is necessary for the normal development of language in the first year of life. Thiamine deficiency was found to affect children’s abilities selectively, yielding specific impairments in the language domains of syntax and lexical retrieval, without conceptual or general cognitive deficits. Thus, this study demonstrates the extreme importance of micronutrients, specifically of thiamine, in the development of brain substrates for language.
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Supplementary material

Supplementary material is available at Brain online.

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